REMARKS

This application was subject to a five-way Restriction Requirement dated June 28, 2002. Applicants elected with traverse to prosecute Group IV, claims 70-82 and 91-92. In the Office Action dated November 1, 2002, the Examiner made the Restriction Requirement final and deemed the non-elected claims 1-69 and 83-90 withdrawn. These claims are canceled without prejudice by the present Amendment, and Applicants reserve the right to file one or more divisional applications claiming the subject matter of these claims.

Upon entry of the present Amendment, claims 70-82 and 91-92 are pending in the application. Claims 74 and 76-81 are currently withdrawn from prosecution due to the species election made in Applicants' Response dated November 22, 2002, as required by the Office Action dated November 1, 2002.

In the amendment submitted herewith, claims 70 and 91 have been amended to specify a pharmaceutical composition that is formulated for topical administration. No new matter has been introduced by this amendment, as support therefor is found throughout the specification, for example, at page 59, lines 18-20; page 60, line 11; and page 62, line 1 – page 70, line 5. Claim 73 has been amended so that the generic structure in sub-part (d) provides antecedent basis for compound II of claim 82. Support for this amendment is found at page 48, lines 3-7 of the specification. Claim 82 has been amended to correct a typographical error in structure III, by changing a CH_3 to CH_2 to properly indicate that the carbon has a valence of 4 rather than 5. The same typographical error has been corrected in structure III in the specification at page 9, line 10 and at page 52, line 10. No new matter has been added by this amendment, which simply clarifies what one of skill in the art would have understood to be the proper structure. Entry of this amendment is respectfully requested.

Each of the rejections set forth in the Office Action mailed on January 27, 2003 is addressed individually below.

Rejection of Claims 70-73 and 91-92 under 35 U.S.C. § 112, first paragraph

Claims 70-73 and 91-92 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner opined that the specification, while being enabling for the elected species of claim 73, does not enable any and all intended compounds in the compositions of the invention. The Examiner also opined that it would take undue experimentation to determine which compounds would yield a composition for reducing skin pigmentation, and referred to Medline 67014260 and Medline 89379530 as disclosing that chlorpromazine, a phenothiazine compound intended for use in the present invention, produces skin pigmentation. Applicants respectfully disagree.

The specification identifies numerous compounds that affect (*e.g.*, reduce) skin pigmentation by the disclosed methods and mechanisms, including compounds that cause an alteration in late endosomal/lysosomal trafficking (*see, e.g.*, pages 43-54). Furthermore, the specification includes sufficient disclosure to enable one of ordinary skill in the art to identify additional compounds that affect pigmentation as claimed. Methods of screening for compounds that affect skin pigmentation by inhibiting or inducing melanogenesis are set forth in detail beginning at page 19, line 19 of the Application. At page 42, lines 5-9, the Application states that the disclosed methods "may be used to identify compounds that effect an alteration in late endosomal/lysosomal trafficking, and therefore, reduce or inhibit melanogenesis and/or pigmentation. Such compounds are also useful as skin lightening agents."

In addition to the general description of assay methods in cultured melanocytes presented at pages 19-42 of the specification, the experimental examples demonstrate specific applications of methods for identifying compounds that reduce skin pigmentation. For example, Example 6 at page 78 of the specification describes experiments in which the effect on melanin production in melanocytes of various compounds that alter late endosomal/lysosomal trafficking was evaluated, and a reduction in melanin was observed. These same techniques could be used to evaluate the effect that other compounds have on melanin production, and to identify those

compounds that reduce melanin production in melanocytes, and thus are expected to reduce skin pigmentation. Thus, the specification clearly includes sufficient enabling disclosure of how to screen for compounds that affect (and in particular reduce) skin pigmentation by affecting melanogenesis, *e.g.*, by causing an alteration in late endosomal/lysosomal trafficking in a skin cell.

Applicants respectfully submit that the references cited by the Examiner regarding the production of skin pigmentation by chlorpromazine are irrelevant to the present invention. As noted in the cited references, skin pigmentation is a rare side effect that has been observed following prolonged therapy with high doses of chlorpromazine, *e.g.*, in schizophrenics. Such therapy with chlorpromazine involves administration of the drug for activity inside the body, generally by oral administration. One cited reference, Medline 67014260 (copy of full reference attached), addresses possible ways to reverse the skin pigmentation side effect of internally administered chlorpromazine. The other cited reference, Medline 89379530 (copy of full reference attached), teaches oral administration of chlorpromazine as part of a possible treatment regimen for vitiligo (a condition resulting in white patches of skin), but discloses that the contributory effect of chlorpromazine, if any, was difficult to determine.

In contrast to these references addressing a possible effect of <u>oral</u> chlorpromazine, Applicants' amended claims are directed to compositions formulated for <u>topical</u> administration. The cited references do not teach or suggest that chlorpromazine would cause skin pigmentation when applied <u>topically</u>, as claimed and described in Applicants' specification. As discussed above, the specification provides detailed disclosure regarding specific compounds for inclusion in the topical compositions of the invention, and methods to identify further such compounds. Thus, the cited references are irrelevant to the claimed invention, and would in no way prevent one of skill in the art from following the clear teachings in the specification identifying numerous compounds that, when included in a topical composition, would reduce skin pigmentation by the disclosed methods and mechanisms, and describing methods for identifying more such compounds.

Accordingly, Applicants respectfully submit that the full scope of amended claims 70-73 and 91-92 is enabled by the specification, such that the present rejection under 35 U.S.C. § 112, first paragraph should be reconsidered and withdrawn.

Rejection of Claims 70-73, 75, and 91-92 under 35 U.S.C. § 112, second paragraph

Claims 70-73, 75, and 91-92 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The various indefiniteness arguments asserted by the Examiner are addressed individually below.

First, the Examiner stated that it is unclear whether a compound of the claimed composition or kit reduces skin pigmentation by altering late endosomal/lysosomal trafficking in a skin cell (claims 70-73, 75, 82) or modulates melanogenesis by inhibiting late endosomal/lysosomal trafficking (claims 91-92). Applicants respectfully disagree.

The two groups of claims identified by the Examiner simply present the invention using slightly different terminology, which is in no way inconsistent or unclear. At page 56, lines 6-7 the specification states that "[t]he invention takes advantage of the discovery that the inhibition of late endosomal/lysosomal trafficking results in a decrease in melanin production in melanocytes." Furthermore, at page 42, lines 7-9, the specification refers to "compounds that effect an alteration in late endosomal/lysosomal trafficking, and therefore, reduce or inhibit melanogenesis and/or pigmentation. Such compounds are also useful as skin lightening agents." Based on such disclosure, claims 70-73, 75, and 82 are definite in reciting compounds that reduce skin pigmentation by altering late endosomal/lysosomal trafficking in a skin cell, and claims 91-92 are equally definite in reciting compounds that modulate melanogenesis, *e.g.*, by inhibiting late endosomal/lysosomal trafficking. The fact that different claim terms of varying scope are employed (*e.g.*, claim 70 recites alteration while claim 91 recites inhibition of late endosomal/lysosomal trafficking, and claim 70 recites reducing skin pigmentation while claim 91 recites modulating melanogenesis) does not render the claims indefinite.

The Examiner also asserted that it is not clear whether the term "alteration" in claim 70 is intended to mean inhibit or activate late endosomal/lysosomal trafficking. Applicants respectfully disagree.

The term "alteration" refers to a difference in late endosomal/lysosomal trafficking, and need not be limited to activation or inhibition. Indeed, the specification refers to compounds that "alter [*i.e.*, change] or inhibit [*i.e.*, restrain] late endosomal/lysosomal trafficking" (emphasis added) (page 46, lines 4-5 and 10-11) and "methods of inhibiting melanogenesis by altering or inhibiting late endosomal/lysosomal trafficking" (emphasis added) (page 55, lines 19-20 and line 30). Thus, the claim term "alteration" need not be limited to inhibition or activation.

Next, the Examiner stated that it is unclear if "modulate" in claims 91 and 92 is intended to mean increase or decrease skin pigmentation. Applicants respectfully disagree.

Claim 91 recites a kit comprising a compound that modulates melanogenesis by affecting P protein function, inhibiting late endosomal/lysosomal trafficking, or inhibiting an ATPase, and claim 92 recites the kit of claim 91 including instructions describing how to use the compound to modulate skin pigmentation. Similarly, at page 70, lines 24-33, the specification discloses a kit comprising one or more compositions that mimic and/or affect P protein function, inhibit late endosomal/lysosomal trafficking, or inhibit ATPases. The disclosed kit optionally includes instructions directing the use of the reagents to "modulate skin pigmentation, *i.e.*, to either lighten or darken skin as appropriate to the particular included composition" (emphasis added). This description makes clear that the term "modulate" in claims 91-92 encompasses both skin lightening, or decreasing skin pigmentation, and skin darkening, or increasing skin pigmentation.

The Examiner opined further that it is unclear whether "contacting the melanocyte" as recited in claim 71 refers to use of the composition *in vivo* or *in vitro*. Applicants respectfully submit that the term "contacting" clearly is a generic term that

can encompass both *in vivo* and *in vitro* use. The specification also discloses both *in vivo* and *in vitro* use (see, *e.g.*, page 61, line 27; page 59, line 34).

It was also asserted that there is no antecedent basis in claim 73 for compound II of claim 82. To overcome this rejection, Applicants have amended the description of the generic structure in sub-part (d) of claim 73 to provide antecedent basis for compound II of claim 82.

Finally, the Examiner stated that compound III of claim 82 is confusing because CH_3 on position 15 gives the carbon a valence of 5. To overcome this rejection, Applicants have amended claim 82 to correct the inadvertently made typographical error in structure III, by changing the CH_3 to CH_2 to properly indicate that the carbon has a valence of 4 rather than 5.

In view of the above-referenced arguments and amendments, Applicants respectfully submit that claims 70-73, 75, and 91-92 are not indefinite, and the rejection of claims 70-73, 75, and 91-92 under 35 U.S.C. § 112, second paragraph should be reconsidered and withdrawn.

Rejection of Claims 70-72 under 35 U.S.C. § 102(b)

Claims 70-72 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by CA126:190762.

Applicants' claim 70, as amended, recites "a pharmaceutical composition for reducing skin pigmentation, comprising a skin pigmentation reducing effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for topical administration."

CA126:190762 discloses the use of pregnenolones as melanin formation inhibitors for skin lightening. The reference does not teach that these compounds cause an alteration in late endosomal/lysosomal trafficking.

To anticipate a claim, a reference must teach every element of the claim. MPEP § 2131. The Examiner admitted that the CA126:190762 does not disclose a topical composition that includes a skin pigmentation reducing effective amount of a

compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell. However, the Examiner argued that a compound that reduces skin pigmentation would inherently possess the properties of Applicants' claimed compositions.

Inherency requires that the alleged inherent characteristic is necessarily present in the prior art. MPEP § 2112. Applicants respectfully submit that the compositions disclosed in CA126:190762 would not necessarily possess the characteristics of Applicants' claimed compositions, which contain a skin pigmentation reducing effective amount of a topically applied compound that effects an alteration in late endosomal/lysosomal trafficking. There are many known compositions that do not effect an alteration in late endosomal/lysosomal trafficking, and yet control or inhibit skin pigmentation by various different mechanisms, for example, by bleaching existing pigment or preventing new pigment synthesis by inhibiting the activity of tyrosinase (see page 4, line 24 – page 5, line 10 of the specification).

In contrast, Applicants' claims 70-72 specifically recite compositions that reduce skin pigmentation by the previously unknown mechanism of effecting an alteration in late endosomal/lysosomal trafficking. Because there are so many other possible mechanisms for affecting skin pigmentation, and because many compounds that affect skin pigmentation do not alter late endosomal/lysosomal trafficking, prior art compositions that reduce skin pigmentation by other or unknown mechanisms would not inherently possess the characteristics of Applicants' claimed compositions.

Thus, because CA126:190762 does not teach compositions containing a compound that effects an alteration in late endosomal/lysosomal trafficking as recited in claim 70, the reference does not anticipate claim 70. Dependent claims 71-72 are drawn to embodiments of claim 70 and thus contain every limitation of claim 70. Because CA126:190762 does not teach every element of claim 70, the reference also does not anticipate claims 71-72. Accordingly, Applicants respectfully submit that the rejection of claims 70-72 under 35 U.S.C. § 102(b) should be reconsidered and withdrawn.

Rejection of Claims 70-73, 75, and 82 under 35 U.S.C. § 102(a) or (b)

Claims 70-73, 75, and 82 were rejected under 35 U.S.C. § 102 (a) or (b) as allegedly being anticipated by CA130:295103 or EMBASE 1998386460.

As described above, Applicants' claim 70, as amended, recites "a pharmaceutical composition for reducing skin pigmentation, comprising a skin pigmentation reducing effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for topical administration."

CA130:295103 is directed to localization of Niemann-Pick C1 protein in astrocytes, and discusses the effect on NPC1 levels of compounds that block cholesterol transport out of lysosomes. EMBASE 1998386460 teaches that bafilomycin A1 and nocodazole affect endocytic transport in HeLa cells. Neither reference teaches a topical composition for reducing skin pigmentation.

The Examiner admitted that the references do not teach a composition for reducing skin pigmentation comprising a compound that effects an alteration in late endosomal/lysosomal trafficking. However, the Examiner argued that it would be inherent that a compound that effects an alteration in late endosomal/lysosomal trafficking would also be able to reduce skin pigmentation.

Applicants respectfully submit that neither CA130:295103 nor EMBASE 1998386460 teaches every limitation of claim 70, either expressly or inherently, because neither reference teaches a composition that is formulated for topical administration and contains a skin pigmentation reducing effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking. Thus, neither of the references anticipates claim 70, or dependent claims 71-73, 75, and 82, which contain every limitation of claim 70. Accordingly, Applicants respectfully submit that the present rejection of claims 70-73, 75, and 82 under 35 U.S.C. § 102 (a) or (b) should be reconsidered and withdrawn.

Rejection of Claims 91-92 under 35 U.S.C. § 103(a)

The Examiner rejected claims 91-92 under 35 U.S.C. § 103(a) as being obvious over CA126:190762, CA130:295103, or EMBASE 1998386460.

Applicants' amended claim 91 recites "a kit comprising a pharmaceutical composition formulated for topical administration, the pharmaceutical composition comprising a pharmaceutically effective amount of a compound that modulates melanogenesis by affecting P protein function, inhibiting late endosomal/lysosomal trafficking, or inhibiting an ATPase."

As described above, CA126:190762 discloses the use of pregnenolones as melanin formation inhibitors for skin lightening. The reference does not teach or suggest that these compounds affect P protein function, inhibit late endosomal/lysosomal trafficking, or inhibit an ATPase.

CA130:295103 is directed to localization of Niemann-Pick C1 protein in astrocytes (*i.e.*, neural cells), and considers the effect on NPC1 levels of compounds that block cholesterol transport out of lysosomes. EMBASE 1998386460 teaches that bafilomycin A1 and nocodazole affect endocytic transport in HeLa cells (*i.e.*, cancer cells). Neither reference teaches a topical composition for modulating melanogenesis in melanocytes.

To support a *prima facie* case of obviousness, the cited references must teach or suggest every element of the claimed invention, and there must be some suggestion or motivation to combine the teachings of the cited references. The motivation to combine must be found in the prior art, and must not be based on impermissible hindsight in view of Applicants' disclosure. MPEP § 2142.

None of the cited references alone teaches or suggests every limitation of Applicants' claim 91. CA126:190762 does not teach or suggest that the disclosed skin lightening compounds affect P protein function, inhibit late endosomal/lysosomal trafficking, or inhibit an ATPase. Because many possible mechanisms exist for modulating melanogenesis, as discussed above, the compounds disclosed by CA126:190762 would not necessarily modulate melanogenesis by the mechanisms

recited in claim 91. Thus, the reference does not teach or suggest every limitation of claim 91 either expressly or inherently. CA130:295103 and EMBASE 1998386460 also do not teach or suggest every limitation of claim 91, because neither reference discloses a topical composition that modulates melanogenesis.

Furthermore, prior to Applicants' invention, there would have been no motivation to combine the teachings of CA130:295103 and EMBASE 1998386460, relating to compounds that affect lysosomal trafficking, with the teachings of CA126:190762, directed to compounds for reducing skin pigmentation. This is because, prior to Applicants' invention, it was not recognized that compounds that alter late endosomal/lysosomal trafficking would have an effect on skin pigmentation. Indeed, the teachings of the cited references that relate to compounds affecting lysosomal trafficking are directed to neural cells and cancer cells, and thus would not be considered equally applicable with respect to skin pigmentation in melanocytes. Thus, the only possible motivation to combine the cited references would be based on improper hindsight in view of Applicants' disclosure.

Thus, because none of the cited references alone teaches every limitation of claim 1, and there would have been no motivation to combine the cited references, *prima facie* obviousness has not been established, and claims 91-92 are not obvious in view of the cited references alone or in combination. Accordingly, Applicants respectfully request that the rejection of claims 91-92 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Information Disclosure Statement

The Examiner requested that Applicants submit an information disclosure statement. Applicants respectfully direct the Examiner's attention to the Information Disclosure Statement filed on December 21, 2001, and the Supplemental Information Disclosure Statement filed on February 4, 2003, copies of which are submitted herewith, along with copies of the returned postcards indicating their receipt by the Patent and Trademark Office. Applicants respectfully request that the Examiner initial and return copies of the enclosed PTO-1449 forms with the next Patent Office Communication. If

the Examiner requires additional copies of the references cited in the information disclosure statements (copies were submitted with the information disclosure statements as originally filed), Applicants will supply copies of the references upon request.

CONCLUSION

In view of the amendments and arguments set forth herein, Applicants respectfully submit that the objections and rejections contained in the Office Action mailed on January 27, 2003 have been overcome, and that all of the pending claims are in condition for allowance.

Applicants hereby petition for a three-month extension of time pursuant to 37 C.F.R. § 1.136 to respond to the Office Action dated January 27, 2003. Please deduct the $930.00 fee for this purpose from our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

Emily R Whelan

Emily R. Whelan
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